(c) at least one of a cyclooxygenase inhibitor, a PGI_2-mimetic, a thromboxane (TXA_2) inhibitor, a compound possessing PGI_2-agonistic and TXA_2-inhibiting properties, a compound possessing TXA_2-antagonistic and PGI_2-mimetic activities, and a TXA_2-antagonist, in amounts effective to ameliorate the symptoms of preeclampsia accompanied or unaccompanied by preterm labor in a pregnant female mammal, dysmenorrhea, or functional uterine bleeding or hemorrhaging.

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REMARKS

Claim 14 has been amended to correct some inadvertent typographical errors. The amendment was not made for purposes of patentability and does not narrow the scope of the claim.

Claim 28 is a duplicate of claim 14, as amended on July 21, 2000 (and further amended herein to correct some typographical errors); it has been canceled.

The withdrawal from consideration of claims encompassing non-elected species

In response to a requirement for an election of species, applicants elected, for compound (a), the progestin, progesterone; for compound (b), the nitric acid donor, nitroglycerin; and for compound (c), the cyclooxygenase inhibitor, aspirin - as recited, *e.g.*, in claims 14, 17-19, 29, and 34-35. In the Office Action of May 1, 2001, claims 15-16, 20-21, 30 and 34-35, drawn to non-elected species, were withdrawn from consideration. The withdrawn claims recite other species of the invention, *e.g.*, for compound (b), an NO synthase substrate, *e.g.*, L-arg, or an NO synthase substrate which is in an amount effective to "raise the blood level of circulating L-arg to at least 1 mmole above the normal circulating level of 2 to 3 nmolar, or an NO donor which is in an amount effective to provide a blood level of about 1-1000 nmole; and

for compound (c), a PGI_2 mimetic, *e.g.*, a thromboxane inhibitor. Applicants respectfully traverse the withdrawal from consideration of the non-elected species. Applicants have the right to have the entirety of the claims examined. By refusing to examine the above-mentioned claims on their merits, applicants are denied the right to have the invention examined.

As is summarized in MPEP 803.02, it is improper to restrict within Markush-type generic claims which include a plurality of alternatively usable substances or members, such as the generic claims of the present invention:

> "In applications containing claims of that nature, the examiner may require a **provisional** election of a single species prior to examination on the merits. The provisional election will be given effect in the event that the Markush-type claim should be found not allowable. **Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentablility. ... [S]hould no prior art be found that anticipates or renders obvious the elelcted species, the search of the Markush-type claim will be extended.** " (emphasis added)

See also *In re Weber et al.*, 198 USPQ 328 (CCPA 1978):

> As a general proposition, an applicant has a right to have *each* claim examined on the merits. If an applicant submits a number of claims, it may well be that pursuant to a proper restriction requirement, those claims will be dispersed to a number of applications. Such action would not affect the right of the applicant eventually to have each of the claims examined in the form he considers to best define his invention. If, however, a single claim is required to be divided up and presented in several applications, that claim would never be considered on its merits. The totality of the resulting fragmentary claims would not necessarily be the equivalent of the original claim.

See also *In re Haas*, 198 USPQ 334 (CCPA 1978).

The Examiner is reminded that consideration of the **entire** scope of the claims is required, and is requested to examine the withdrawn claims.

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The rejection over U.S. Patent No. 5,508,045 ("Harrison")

The rejection over Harrison as allegedly rendering the claimed invention obvious is unwarranted. Harrison does not disclose or suggest a pharmaceutical composition comprising, *e.g.*, a progestin (compound (a)), a nitric acid substrate or donor (compound (b)), **and** at least one of a cyclooxygenase inhibitor, a PGI_2-mimetic, a thromboxane (TXA_2) inhibitor, a compound possessing PGI_2-agonistic and TXA_2-inhibiting properties, a compound possessing TXA_2-antagonistic and PGI_2-mimetic activities, or a TXA_2-antagonist (compound (c)). At best, Harrison discloses a composition which comprises a nitric oxide substrate or donor (applicants' component (b)) and the **optional** presence of one or more other agents, such as a tocolytic agent, among which can be found compounds which can be, *e.g.*, applicants' compounds (a) or (c). There is no disclosure or suggestion of a composition comprising **three** distinct agents, especially not comprising the specific agents of the instant claims, and certainly not comprising the instant elected species.

Harrison discloses a laundry list of optional agents which can be present, in addition to applicants' component (b), in its composition. These optional agents include, *e.g.*, the generic categories of "other tocolytic agents, analgesics, [and] vasopressors" (col. 20, lines 57-59). Among the wide variety of tocolytic agents listed are "β-adrenergic agonists, oxytocin antagonists, prostaglandin synthesis inhibitors such as prostaglandin synthase inhibitors, magnesium salts, calcium transport blockers, ethanol, [and] phosphodiesterase inhibitors" (col. 21, lines 226-31). Among the wide variety of prostaglandin synthesis inhibitors listed are,

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e.g., "indomethacin, naproxen, meclofenamic acid, phenylbutazone, analogues thereof and other agents." (col. 21, lines 54-58). Harrison provides no guidance (motivation) to select the particular components (a) and (c) recited in the instant claims (*e.g.*, progesterone and aspirin) from the myriad of compounds disclosed in Harrison. Absent such guidance, the reference does not render the claimed invention obvious. *In re Jones*, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Baird*, 29 USPQ2d 1550 (Fed. Cir. 1994).

Moreover, the treatment indication of Harrison's composition (*e.g.*, control of preterm labor) is different from applicants.' Harrison does not disclose or suggest a composition for treating preeclampsia accompanied or unaccompanied by preterm labor, dysmenorrhea, or functional uterine bleeding or hemorrhaging. In fact, Harrison does not even disclose or suggest preterm labor as part of the preeclampsia syndrome, and actually explicitly teaches away from using tocolytic agents (for labor inhibition) in the case of preeclampsia. See, *e.g.*, column 2, lines 4-13 ("contraindications such as eclampsia, preeclampsia ..."). Therefore, neither Harrison nor what was known to one of skill in the art would have provided motivation to modify Harrison's composition to arrive at applicants' claimed composition. That is, there was no motivation to achieve a composition which includes, in addition to compound (b), both compounds (a) and (c). Absent such motivation, with the requisite reasonable expectation of success, the reference does not render obvious the claimed invention. *In re Vaeck*, 20 USPQ 1438 (Fed. Cir. 1991).

Withdrawal of the rejection is therefore respectfully requested.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

14. (Four Times Amended) A pharmaceutical composition comprising an admixture of effective amounts of:

(a) a progestin and

(b) a nitric oxide synthesis substrate, a nitric oxide donor or both, and,

(c) at least one of a cyclooxygenase inhibitor, a PGI_2-mimetic, a thromboxane (TXA_2) inhibitor, ~~a PGI_2-mimetic, a thromboxane (TXA_2) inhibitor,~~ a compound possessing PGI_2-agonistic and TXA_2-inhibiting properties, a compound possessing TXA_2-antagonistic and PGI_2-~~memetic~~ mimetic activities, and a TXA_2-antagonist, in amounts effective to ameliorate the symptoms of preeclampsia accompanied or unaccompanied by preterm labor in a pregnant female mammal, dysmenorrhea, or functional uterine bleeding or hemorrhaging.

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